## REMARKS

Claims 30-49 are pending in the application. Favorable reconsideration in light of the enclosed Rule 132 Declaration and the remarks which follow is respectfully requested.

### I. Rejection Under 35 U.S.C. § 102(e)

Claims 30-49 have been rejected under 35 U.S.C. § 102(e) over Reich *et al* (U.S. Patent No. 6,090,995). Reich *et al* relates to synthetic surfaces having a surface modifier composition attached thereto, and an epithelial cell supporting coating on the surface modifier composition. The surface modifier composition is a polymer with a plurality of pendant groups, and the pendant groups are functionalized so that they covalently bond to the synthetic surface. The epithelial cell supporting coating may contain collagen, fibronectin, laminin, heparin, heparin sulfate proteoglycan, and chondroitin sulfate, among others. The functionalized pendant groups of the surface modifier composition also serve to bind the epithelial cell supporting coating.

The Examiner contends that Reich *et al* uses the same materials (such as collagen and heparin sulfate) and that the materials are hemocompatible.

To establish anticipation, each and every claim feature must be disclosed in a single cited art document. Claims 30, 39, and 47 require a hemocompatible surface containing a constituent of an outer layer of a blood cell or a mesothelial cell or a combination thereof. Reich *et al* fails to disclose a hemocompatible surface containing a constituent of an outer layer of a blood cell or a mesothelial cell or a combination thereof. While Reich *et al* discloses certain materials, none of the materials listed by Reich *et al* are obtained from an outer layer of a blood cell or a mesothelial cell. Since Reich *et al* does not disclose all of the claimed features, and especially any material from an outer layer of a blood cell or a mesothelial cell, Reich *et al* cannot anticipate claims 30-49.

**A. The Rule 132 Declaration**

In support of the fact that the constituent of a blood cell or a mesothelial cell required by claims 30, 39, and 47 is different from the materials of Reich *et al*, a Rule 132 Declaration is enclosed. Specifically, experiments were performed to demonstrate the differences of constituents obtained from an outer layer of a blood cell or a mesothelial cell versus like named compounds that are not obtained from a blood cell or a mesothelial cell. The experiments show the hemocompatible potential of substances isolated from erythrocytes and mesothelial cell glycocalices in relation to materials not obtained from blood cells or mesothelial cells.

The constituent of blood cells or mesothelial cells as well as the materials of Reich *et al* were covalently immobilized on cellulose membranes and then subjected to *in vitro* blood tests in order to determine blood platelet adhesion on the membrane surface. Measuring platelet adhesion is a well-established method to determine the thrombogenicity of foreign surfaces. A high number of deposited thrombocytes means low hemocompatibility while low or no deposition of thrombocytes means high hemocompatibility.

The test results clearly show that constituents of blood cells or mesothelial cells are different from the materials of Reich *et al.* Both groups of materials are subjected to the same preparation and experimental conditions. The hemocompatibility of the claimed materials (~0% coverage) is superior to that of materials that are NOT constituents of blood cells or mesothelial cells *(See* Figure on Page 6 in Rule 132 Declaration). For example, commercially available material heparin sulfate from swine intestinal mucosa (HS) exhibited moderate thrombocyte adhesion (10% coverage). This moderate thrombocyte adhesion is insufficient to establish hemocompatibility, and thus the claimed materials are not only different from, but also superior to materials mentioned by Reich *et al* that are not constituents of blood cells or mesothelial cells.

**B. Substantial Differences From Reich *et al***

Reich *et al* fails to teach or suggest the hemocompatibility (neither activating nor suppressing a blood coagulation system) required in claims 30, 39, and 47 that results from the use of materials obtained from outer layers of blood cells, outer layers of mesothelial cells. The Examiner states that according to Reich *et al*, the use of heparin sulfate (a polysaccharide constituent of an outer layer of a blood cell) to achieve hemocompatibility would be obvious to one skilled in the art, and that how or where the heparin sulfate is obtained is not given patentable weight. Applicants respectfully disagree for at least the following five additional reasons.

First, the heparin sulfate materials used in the claimed materials are structurally distinct from commercially available heparin sulfate materials. The specification clearly indicates that heparin sulfates are included in the hemocompatible surfaces as the oligosaccharide or polysaccharide substituents of proteoglycans (page 6, lines 21-26 of the specification). Proteoglycans are macromolecules formed from a core protein and at least one, but frequently more (perhaps up to tens or hundreds) carbohydrate chains. The heparin sulfate materials of the claims are substituents of proteoglycans or parts of proteoglycans, not isolated oligosaccharides or polysaccharides. In short, the materials of the claims have both carbohydrate and protein substituents. Commercially available heparin sulfate materials are isolated oligosaccharides or polysaccharides without protein substituents. Therefore, the materials of the claims have a different structural composition than commercially available heparin sulfate materials.

Second, the distribution of molecular weights in the native materials differs from the commercially available materials, even if commercially available heparin sulfate materials have substantially similar chemical composition as native heparin sulfate materials. Native heparin sulfate comprises a wider range of molecular weights (about 6 to about 40 kiloDaltons) than most commercial heparin sulfate preparations (generally about 12 to about 16 kiloDaltons). Accordingly, the size distribution of a heparin sulfate material derived from the outer layer of a blood cell or a mesothelial cell is broader than

that of a commercially derived heparin sulfate material. The broader size distribution of native heparin sulfate leads to a closer approximation of native conditions than is possible with commercially available heparin sulfate.

Third, the two materials would not be substantially the same if one were to combine commercially available heparin sulfate materials into a mixture with a molecular weight distribution approximating that of native heparin sulfate materials. The native heparin sulfate materials contains trace impurities that come from other constituents of the outer layer of a red blood cell and/or mesothelial cell. These trace impurities may be phospholipids, membrane proteins, polysaccharides, other glycosaminoglycans, etc. Without wishing to be bound by any particular theory, these trace impurities may play a role in achieving hemocompatibility, even if identities and hemocompatibility-enhancing functions are unknown. On the other hand, commercially available heparin sulfate materials are either completely purified and isolated from other materials, or processed for a purpose other than forming a hemocompatible surface. Commercially available heparin sulfate materials therefore contain fewer trace impurities of that come from other constituents of the outer layer of a red blood cell and/or mesothelial cell. Furthermore, commercially available heparin sulfate materials may contain a higher level of non-native materials commonly used in commercial preparations, such as buffer molecules, salts, metal chelators, etc. These differences directly lead to differences in hemocompatibility.

Fourth, Reich *et al* is primarily concerned with incorporating into the surface modifier compositions biological materials which are known to support growth, migration and attachment of epithelial cells (*See* Column 4, Lines 52-55; Claims 4 and 11). One skilled in the art would therefore interpret Reich *et al* to describe a general method for fixation of a device relative to other tissues and/or for cosmetic purposes, and a specific method for subepithelial implantation and epikeratophakia lenses. Claims 30, 39, and 47 describe the required hemocompatibility, which does not involve fixation of a device relative to other tissues and/or cosmetic purposes. Additionally, to achieve the desired

hemocompatibility, one must avoid incorporating materials that support growth, migration, and attachment of epithelial cells. Hemocompatibility requires that few if any cells in the blood coagulation system interact with a given device such that the blood coagulation system is not activated nor suppressed. It is noted that hemocompatibility is neither explicitly mentioned nor suggested by Reich *et al.*

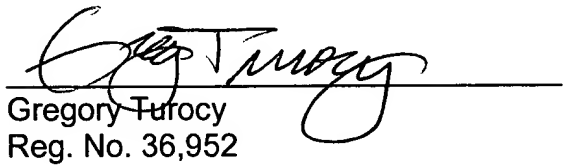
Fifth, Reich *et al* envisions a device being coupled with biological materials selected from the group consisting of antibiotics, antimicrobial agents, antiviral agents, anti-inflammatory agents, anti-protease agents, hormones, vitamins, analgesics, chelating agents, and mitogenic agents (*See* Claims 5 and 12). Each of these biological materials is commercially available and has a pharmaceutical effect. The claimed materials are neither commercially available nor intended to have any pharmaceutical effect. For example, coupling the device with material derived from the glycocalix has the effect of making the device behave more like the surrounding tissue, rather than having any pharmaceutical effect, such as anti-microbial activity (*See* Page 6, Lines 27-29). Claims 30,39, and 47 recite that the hemocompatible surface does neither activate nor actively suppress a blood coagulation system. Thus, hemocompatibility is not a pharmaceutical effect and consequently hemocompatibility is not obvious from Reich *et al.*

Should the Examiner believe that a telephone interview would be helpful to expedite favorable prosecution, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

In the event any fees are due in connection with the filing of this document, the Commissioner is authorized to charge those fees to our Deposit Account No. 50-1063.

Respectfully submitted,

**AMIN & TUROCY, LLP**



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**CERTIFICATE OF MAILING (37 CFR 1.8a)**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to: Commissioner for Patents; Mail Stop Amendment; P.O. Box 1450; Alexandria, VA 22313-1450

Rebecca A. Bellas
(Type or print name of person mailing paper)

May 24, 2005 Rebecca A. Bellas

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re patent application

| | | | |
|---|---|---|---|
| Applicant: | Horres, et al. | Art Unit: | 3738 |
| Serial No.: | 09/914,241 | Examiner: | Thomas C. Barrett |
| Filed: | August 24, 2001 | | |

Title: HEMOCOMPATIBLE SURFACES AND METHOD FOR PRODUCING SAME

**DECLARATION UNDER 37 C.F.R. § 1.132**

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Erika Hoffmann, declare and say as follows:

I hold a Bachelor's degree from the Technical University of Aachen, Germany, a Master's degree from the Technical University of Aachen, Germany, and in the near

future a Ph.D. degree from the Technical University of Aachen, Germany. I have worked in biotechnology research for over five years and have extensive experience in the field.

I am the inventor of the invention described and claimed in the above-identified patent application and, therefore, I am thoroughly familiar with the subject matter of the invention.

Certain claims of the above-identified patent application stand rejected for lacking novelty over U.S. Patent 6,090,995.

Experimental tests were conducted by me in order to demonstrate that the claimed hemocompatible surface is indeed novel and thus different from the surface modifying composition described in U.S. Patent 6,090,995. U.S. Patent 6,090,995 describes the incorporation of biological materials into the surface modifier composition of a device, the biological materials including heparin or heparin sulfate proteoglycan.

**1. Introduction**

These experiments were performed to demonstrate the differences of a constituent obtained from an outer layer of a blood cell or an outer layer of a mesothelial cell versus like named constituents that are not obtained from a blood cell or a mesothelial cell. Accordingly, the hemocompatible potential of the substances isolated from erythrocytes and mesothelial cell glycocalices was investigated in relation to materials not obtained from a blood cell or a mesothelial cell.

**a. Experimental Organization**

The substances were covalently immobilized on cellulose membranes and then used for in vitro blood tests in order to determine blood platelet adhesion on the membrane surface. Measurement of platelet adhesion is a well-established method to

test the thrombogenicity of foreign surfaces. A high number of deposited thrombocytes means low hemocompatibility; low or no deposition of thrombocytes means better or high hemocompatibility.

The results were compared to the results from several commercially available glycosaminoglycans of different origin treated by the same procedure. The following eight commercially available glycosaminoglycans were used in the trials:

**Materials <u>not obtained</u> from outer layers of erythrocytes and/or mesothelial cells (Commercially available glycosaminoglycans)**

| | |
|---|---|
| Chondroitin sulfate isolated from shark and whale cartilage (Sigma) | = ChS (shark) |
| Chondroitin sulfate from swine blood plasma | = ChS (swine) |
| Keratan sulfate from bovine cornea (gift) | = KS |
| Dermatan sulfate from swine chord (Sigma) | = DeS |
| Heparine from swine intestinal mucosa (Serva) | = Hep |
| Heparan sulphate from swine intestinal mucosa (Sigma) | = HS |
| Hyaluronic acid from human umbilical cord (Sigma) | = HA |

The applicant provided the following materials to compare hemocompatibility:

**Materials obtained from outer layers of erythrocytes and/or mesothelial cells (Claimed materials)**

| | |
|---|---|
| Endothelial cell surface heparansulfate (ESHS) from bovine aortae (produced by the Applicant) | = ESHS |
| Erythrocyte glycolcalix | = EryGlyco |
| Mesothelial glycocalix | = MesoGlyco |

## 2. Experimental Procedure

### a. Functionalization of Cellulose-Membranes for the Coupling Reaction:

The membranes were kept in a stirred mixture of ethanol/water (1:1) for 30 minutes followed by exposure to a 2% solution of 3-amino-propyl-triethoxysilane in ethanol/water (1:1) over night at 45°C. The functionalized membranes were rinsed with distilled water for 30 minutes, stored in ethanol/water (1:1) for 30 minutes at 45°C, and then washed thoroughly with water.

The 3-amino-propyl-triethoxysilane-cellulose membranes were deposited in 0.1 M 2-(N-morpholino)-ethanesulfonic acid buffer having pH 4.75. After cooling to 4°C, a solution of 0.1 % adipinic acid was added and N-cyclohexyl-N´-2-(morpholinoethyl)-carbodiimide-methyl-p-toluenesulfonate was dissolved in the buffer solution in several portions during 6 hours, until reaching a concentration of 2%. The next day, the membranes were washed as follows: first with buffer solution, ice-cooled water, 4 M NaCl and then again extensively with water.

### b. Immobilization procedure:

The aminated and carboxylated membranes were immersed in a 4°C cold solution of 0.1% cyclohexyl-N´-2-(morpholinoethyl)-carbodiimide-methyl-p-toluolsulfonate in 0.1 M 2-(N-morpholino)-ethanesulfonic acid buffer at pH 4.75 and stirred for 30 minutes. After dipping in ice-cooled water for 60 seconds, they were stirred in the 0.1M 2-(N-morpholino)-ethanesulfonic acid buffer at pH 4.75 containing the substance in a concentration of 1 mg/ml buffer solution for 18h at 4°C. The next day, the membranes were washed with buffer solution, ice-cooled water, 4 M NaCl and again extensively with water.

**c. Platelet adhesion test:**

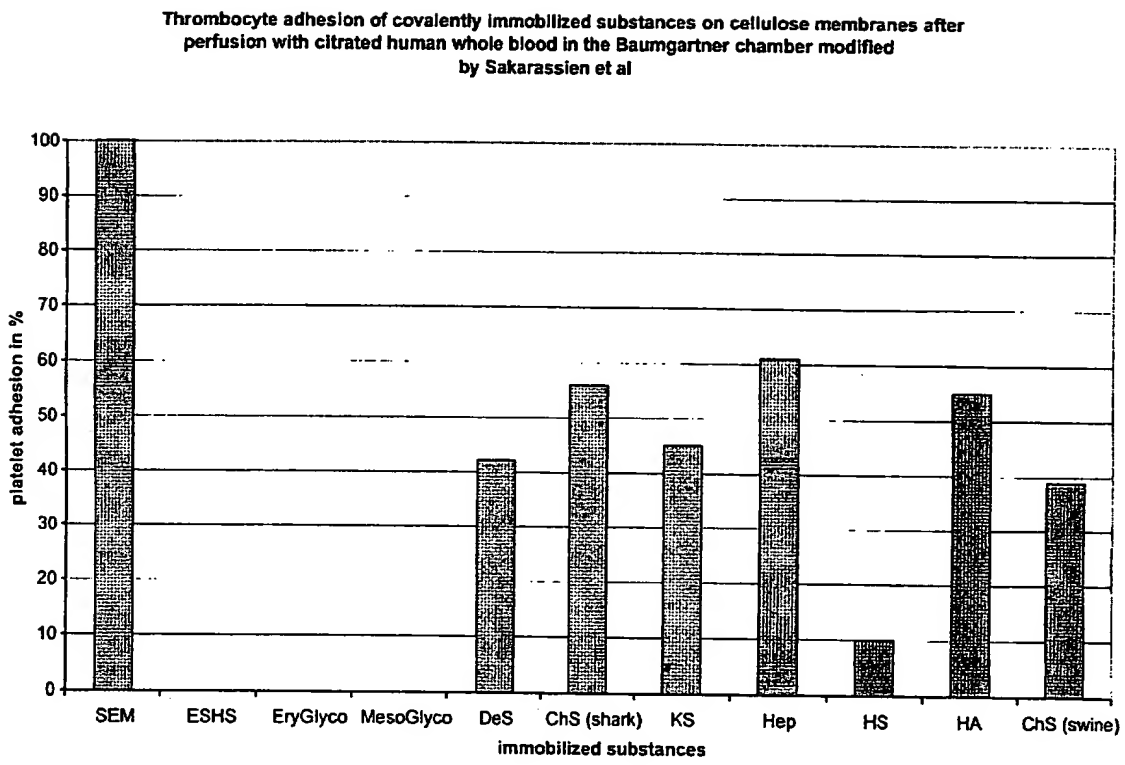
The membranes were perfused at laminar flow and shear rates of 1050 $s^{-1}$ with citrated human whole blood in a Baumgartner perfusion chamber modified by Sakariassen et al (See J. Lab. Clin. Med. 1983, *102*, 522) for 10 minutes. Highly thrombogenic subendothelial matrix (SEM) was perfused as reference.

After fixing the adhering thrombocytes onto the membranes with glutardialdehyde, they were stained with eosin methylene blue solution (May-Grünwald solution and Giemsa solution obtained from Merck Diagnostica). The membranes were analyzed with a light microscope at 400 fold magnification. The thrombocyte adhesion is expressed as percentage platelet coverage in reference to the subendothelial matrix (SEM), given as 100%.

**3. Results**

Results are shown in the table below, and graphically on the next page. Commercial materials are in plain text, and **applicant's materials are in bold text.**

| Material | % coverage |
|---|---|
| Chondroitin sulfate from shark/whale cartilage (Sigma) (ChS (shark)) | - 56% |
| Chondroitin sulfate from swine blood plasma (ChS (swine)) | - 39% |
| Keratan sulfate from bovine cornea (KS) | - 45% |
| Dermatan sulfate from swine chord (DeS) | - 42% |
| Heparine from swine intestinal mucosa (Serva) (Hep) | - 61% |
| Hyaluronic acid from human umbilical cord (Sigma) (HA) | - 55% |
| Heparan sulphate from swine intestinal mucosa (HS) | - 10% |
| **Endothelial cell surface heparansulfate from bovine aortae (ESHS)** | **- ~0%** |
| **Erythrocyte glycocalix (EryGlyco)** | **- ~0%** |
| **Mesothelial cell glycocalix (MesoGlyco)** | **- ~0%** |




## 4. Discussion

The platelet adhesion results for the components of mesothelial cell glycocalix (MesoGlyco) and erythrocyte glycocalix (EryGlyco) are in the same range with the non-thrombogenic and highly hemocompatible endothelial cell surface heparansulfate (ESHS). The components of mesothelial cell glycocalix (MesoGlyco) and erythrocyte glycocalix (EryGlyco) as well as the endothelial cell surface heparansulfate (ESHS) are compounds which come in direct contact with blood and are required for the device surface to be hemocompatible. Consequently, the compounds can be used in the coating procedures in order to obtain the hemocompatible surfaces claimed in this invention.

The heparan sulfate from swine intestinal mucosa (HS) is not as hemocompatible as the components of mesothelial cell glycocalix (MesoGlyco) and erythrocyte glycocalix (EryGlyco). The heparan sulphate from swine intestinal mucosa (HS) shows moderate hemocompatibility (10%). However, in order to obtain the *highly* hemocompatible surfaces of the subject invention, the moderate hemocompatibility of the heparan sulfate from swine intestinal mucosa (HS) is insufficient. Consequently, heparan sulfate isolated from swine intestinal mucosa (HS) is not one of the substances encompassed within the claims of the invention.

All of the other commercially available glycosaminoglycans exhibit insufficient hemocompatibility. The figure shows clearly that use of these compounds does not render a surface sufficiently hemocompatible.

The present test results prove that of the broad group of glycosaminoglycans, only a few are able to solve the problem addressed by the subject invention, namely to make artificial surfaces hemocompatible. In this connection, these few compounds are the components of mesothelial cell glycocalix (MesoGlyco) and erythrocyte glycocalix (EryGlyco) as disclosed in the present invention.

I, Erika Hoffmann, hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued therein.

E. Hoffmann

Erika Hoffmann, Ph.D.

20.05.2005

Date